View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by Elsevier - Publisher Connector



# Outcome of Surgical Resection for Pathologic N0 and Nx Non-small Cell Lung Cancer

*Raymond U. Osarogiagbon, MBBS, FACP,*† Jeffrey W. Allen, MD,*† Aamer Farooq, MD,† Allen Berry, MD,‡ David Spencer, MD,§ and Thomas O'Brien, MD‖*

**Purpose:** Metastasis to lymph nodes (LNs) connotes poor prognosis in non-small cell lung cancer (NSCLC). Sufficient LNs must be examined to accurately determine LN negativity. Patients with no LNs examined (pNx) have an indeterminate stage, may have undetected disease and erroneous assignment to a low-risk group. To evaluate this possibility, we compared the survival of patients with node-negative disease and at least one LN examined (pN0) to those with pNx.

**Methods:** Retrospective analysis of all resections for NSCLC from January 1, 2004 to December 31, 2007 at hospitals in the Memphis Metropolitan Area.

**Results:** Of 746 resections, 90 (12.1%) were Nx; 506 (67.8%) N0. Demographic and histologic characteristics were similar. A total of 54.4% Nx patients had sublobar resection, compared with 5.5% N0 ($p < 0.0001$). In the N0 cohort, the median (range) number of LNs was 5 (1–45); N1 LNs, 3 (0–38); N2 LNs, 1 (0–29); 35.4% had no mediastinal LNs examined; 9.1% had only mediastinal LNs. Eighty-five percent of N0 patients had less than 10 LNs. The 3-year survival estimate for the T1NxM0 versus T1N0M0 patients was 70% versus 79% ($p = 0.17$); for T2NxM0 versus T2N0M0, it was 25% versus 65% ($p < 0.01$).

**Conclusions:** A high percentage of patients undergoing surgical resection for NSCLC have no LNs examined, most of these patients have had sublobar resection. Majority with node-negative disease have fewer than 10 LNs, a large proportion have no mediastinal LNs, raising the possibility of understaging. Patients with pT2Nx do significantly worse than those with pT2N0.

**Key Words:** Quality of care, Lymph node staging, Survival, Surgical resection, Outcomes research, Early stage.

(*J Thorac Oncol.* 2010;5: 191–196)

*Division of Hematology/Medical Oncology, †Department of Medicine, University of Tennessee Health Sciences Center; ‡Department of Pathology, St. Francis Hospital; §Trumbull Laboratories LLC; and ‖Duckworth Pathology Group, Memphis, Tennessee.

Disclosure: The authors declare no conflicts of interest.

Address for correspondence: Raymond U. Osarogiagbon, MBBS, FACP, Division of Hematology/Medical Oncology, Department of Medicine, University of Tennessee Health Sciences Center, 1331 Union Avenue, Suite 800, Memphis, TN 38104. E-mail: rosarogi@utmem.edu

Presented at the American Society of Clinical Oncology Annual Meeting, Orlando, FL, May 30, 2009. Abstract #7513.

Copyright © 2010 by the International Association for the Study of Lung Cancer

ISSN: 1556-0864/10/0502-0191

Lymph node metastasis is the most important determinant of long-term prognosis after surgical resection of non-small cell lung cancer (NSCLC). Five-year survival rates for patients with pathologic N0, N1, N2, and N3 NSCLC are 56%, 38%, 22%, and 6% respectively.[1] Noninvasive evaluation of lymph node (LN) status, clinical N staging, is unreliable.[2,3] Although clinically useful, radiologic studies such as computed tomography and positron emission tomography/computed tomography scans, have significant sensitivity and specificity limitations.[4,5] It is not surprising, therefore, that pathologic staging obtained at thoracotomy is significantly more accurate than radiologic staging.[6] This is reflected in the higher survival statistics of pathologically staged patients over clinically staged patients of identical stage.[7,8]

Furthermore, size of neither the primary tumor[9,10] nor the LN[11,12] is a sufficiently reliable predictor of metastatic LN involvement to justify elimination of mediastinal LN examination below a size threshold.[13] Small LNs frequently contain metastatic disease, and large LNs might be reactive. LNs with metastatic cancer might not feel different than those without. Even micrometastatic LN disease is predictive of adverse prognosis.[14]

Given the importance of pathologic stage in determining prognosis and postoperative adjuvant therapy, and the difficulty in predicting the likelihood and extent of LN involvement, it is believed that curative-intent surgery for lung cancer requires that as many hilar/intrapulmonary (N1) and mediastinal (N2) LNs as possible should be examined after resection to accurately determine the pathologic stage and, possibly, to avoid leaving involved LNs behind.[15] This belief is supported by the significant correlation between the number of LNs examined after lung cancer resection and outcomes, both for node-negative[16,17] and node-positive patients.[18] The American Joint Committee on Cancer (AJCC) tumor, node, metastasis staging system recognizes that involvement of N2 nodes connotes a worse prognosis than involvement of N1 nodes. However, the number of LNs involved is also a powerful predictor of prognosis, irrespective of N1 or N2 location.[18–20] This fact is not currently reflected in the AJCC tumor, node, metastasis staging system.

Analyses of the correlation between the number of LNs examined and outcomes have usually excluded patients who had no LNs examined (pathologic Nx).[16] In clinical practice, these patients are often treated as though they had N0 disease, because of the prohibitive risk of reattempting a more exten-



Copyright © 2010 by the International Association for the Study of Lung Cancer.

sive lymph nodal dissection. Surgical resection without LN harvest introduces needless uncertainty into staging and runs the risk of leaving disease behind.

We compared the characteristics and outcomes of patients who underwent surgical resection for NSCLC with no LNs examined (pNx) to patients of similar T and M stages who had at least one LN examined (pN0) in the Memphis Metropolitan Area Quality of Surgical Resection (MMA-QSR) cohort. Our goal was to estimate the prevalence of suboptimal nodal staging, as well as the circumstances and risk associated with this practice. The study was approved by the Institutional Review Board (IRB) of the University of Tennessee Health Sciences Center, as well as the IRB of all hospitals where surgery was performed. All IRBs provided a waiver of informed consent for this study.

## METHODS

### Patients

We retrospectively analyzed the clinical records of all patients who underwent surgical resection for lung cancer in the greater Memphis Metropolitan Area from January 1, 2004 to December 31, 2007. Patients were identified through a search of pathology databases at hospitals in the Memphis Metropolitan Area. Patients who had lung resection for benign and nonlung primary metastatic disease and those who had preoperative chemotherapy or radiotherapy were excluded from this analysis. Those with bronchioloalveolar cell, small cell, and carcinoid tumors were excluded from the analysis of survival. Death information was obtained from hospital records and search of the National Death Index by trained clerical staff.

### Statistical Analysis

Variables were compared with the $\chi^2$ test or Fisher's exact test. Group medians were compared using the Wilcoxon-Mann-Whitney *U* test. Survival estimates were calculated by the Kaplan-Meier method and compared using the log-rank test. The Cox proportional hazards model was used to compare the hazard between N-stage groups while controlling for other variables. The *p* values less than 0.05 are considered statistically significant and no adjustments have been made for multiple comparisons.

## RESULTS

There were 806 surgical resections for lung cancer in the MMA-QSR cohort during the period of interest. Sixty patients (7.4%) who had received preoperative chemotherapy and/or radiation therapy were excluded from analysis because of the possible impact of such treatment on the pathologic stage of disease, leaving a total of 746 patients in the analysis cohort. Five hundred six patients (67.8%) had at least one LN examined and no LN metastasis (pN0); 90 patients (12.1%) had surgical resection and no LNs examined (pNx). The remaining 150 patients (20.1%) had node-positive disease. These patients are excluded from further discussion.

### Patient Demographics and Disease Characteristics

The demographic characteristics were identical between patients who underwent surgical resection with negative LN examination and those who had no LNs examined (Table 1). The median age of the pN0 cohort was 68.1 (range, 42.0–89.4) years, and that of the pNx cohort was 69.8 (36.9–87.1) ($p = 0.20$). There was no difference in the histologic pattern of disease between patients in the two groups. Most patients had adenocarcinoma and squamous cell carcinoma; 6.5% of patients with pN0 had bronchioloalveolar cell carcinoma, compared with 10.0% of patients with pNx. As expected in a surgical resection cohort, few patients had small cell lung cancer.

There were differences in the T-stage characteristics of patients. Although 87.8% in the N0 and 90.0% of patients in

**TABLE 1.** Characteristics of 596 Patients with Pathologic Nx or N0 Lung Cancer

| Variable | N0 (*N* = 506) *n* (%) | Nx (*N* = 90) *n* (%) | *p* |
|---|---|---|---|
| Age, yr | | | 0.49 |
| <45 | 8 (1.6) | 2 (2.2) | |
| 45–70 | 292 (57.7) | 46 (51.1) | |
| >70 | 206 (40.7) | 42 (46.7) | |
| Gender | | | 0.16 |
| Female | 240 (47.4) | 50 (55.6) | |
| Male | 266 (52.7) | 40 (44.4) | |
| Race | | | 1.00 |
| African American | 106 (21) | 19 (21.1) | |
| White | 397 (78.5) | 71 (78.9) | |
| Other | 3 (0.6) | 0 (0) | |
| Health insurance status | | | 0.93 |
| Commercial | 153 (30.2) | 29 (32.2) | |
| Medicaid | 23 (4.6) | 4 (4.4) | |
| Medicare | 304 (60.1) | 54 (60) | |
| None/other | 26 (5.1) | 3 (3.3) | |
| Histology | | | 0.9 |
| Adenocarcinoma | 218 (43.1) | 39 (43.3) | |
| Squamous | 192 (37.9) | 32 (35.6) | |
| Bronchioloalveolar | 33 (6.5) | 9 (10) | |
| Large cell | 26 (5.1) | 2 (2.2) | |
| Adenosquamous | 15 (3.0) | 4 (4.4) | |
| Other | 16 (3.2) | 1 (1.1) | |
| Small cell | 6 (1.2) | 3 (3.3) | |
| Stage | | | 0.0006 |
| T1 | 250 (49.4) | 65 (72.2) | |
| T2 | 194 (38.3) | 16 (17.8) | |
| T3 | 18 (3.6) | 3 (3.3) | |
| T4 | 40 (7.9) | 4 (4.4) | |
| TX | 4 (0.8) | 2 (2.2) | |
| M1 | 4 (0.8) | 2 (2.2) | |
| M0 | 502 (99.2) | 88 (97.8) | |
| Extent of resection | | | <0.0001 |
| Bilobectomy | 32 (6.3) | 1 (1.1) | |
| Lobectomy | 406 (80.2) | 40 (44.4) | |
| Pneumonectomy | 40 (7.9) | 0 (0) | |
| Segmentectomy | 9 (1.8) | 2 (2.2) | |
| Wedge resection | 19 (3.8) | 47 (52.2) | |


Copyright © 2010 by the International Association for the Study of Lung Cancer

Copyright © 2010 by the International Association for the Study of Lung Cancer.

the pNx group had pT1/pT2 disease, a higher proportion of patients in the pNx group had pT1 lesions (72.2% versus 49.4%), whereas more patients in the pN0 group had pT2 lesions (38.3% versus 17.8%). These differences were statistically significant ($p < 0.001$). The proportion of patients with T3 and T4 diseases was equally small in both groups of patients (Table 1).

## Details of Surgery

All operations were performed by surgeons who were board certified in cardiothoracic surgery. No patients in the cohort had their lung resection surgery performed by general surgeons or nonboard-certified surgeons. The extent of surgical resection was significantly different between the two groups (Table 1). A higher proportion of patients in the pNx cohort had sublobar (either wedge or segmental) resection, 54.4% compared with 5.8% ($p < 0.0001$). There were no pneumonectomies performed in the pNx group and 40 (7.9%) in the pN0 group. Interestingly, 45% of the pNx group had adequately extensive lung resection (bilobectomy or lobectomy) to suggest that intrapulmonary (N1) LNs should have been present in the resection specimen, even if no mediastinal LNs were submitted by the surgeon. This raises questions about the contribution of pathologists to suboptimal LN examination.

The details of LN examination in the pN0 group are presented in Table 2. The overall number of LNs examined was relatively low, with a median of 5. The median number of N2 LNs examined in the pN0 cohort was only 1, and 35.4% of patients had no mediastinal LN material examined, potentially exposing them all to the danger of underestimation of pN stage. Curiously, 9% of patients with pN0 disease had no N1 LNs examined, not only potentially missing N1 disease but also again raising the question of thoroughness of pathologic examination, because 35 of 46 of these patients (76.1%) had sufficiently extensive lung resection to suggest that intrapulmonary (stations 12–14) LNs would be present in the lung resection specimen, irrespective of the surgeon's effort to specifically isolate them. Only 55.5% of pN0 patients had LNs examined from both N1 and N2 LN stations, despite this being the recommended extent of LN examination. However, even this group had a median of only seven LNs examined overall. In fact, 21% of pN0 patients had only 1 or 2 LNs examined and 85% had 10 or fewer LNs examined.

## Outcomes

The overall survival estimates of the two groups are compared in Table 3. The 30-day survival (standard error) of patients in the pNx versus pN0 group was 0.95 (0.03) and 0.96 (0.01), respectively. The unadjusted 3-year survival of patients in the pNx versus pN0 group was 0.62 (0.07) versus 0.70 (0.02). This difference was not significant (log-rank $p$ value = 0.19). When adjusted for T stage (Figure 1), the 3-year survival estimate for the T1NxM0 versus T1N0M0 patients was 70% versus 79% ($p = 0.17$); for T2NxM0 versus T2N0M0, it was 25% versus 65% ($p < 0.01$). There were too few patients with T3NxM0 and T4NxM0 for survival comparison. In the Cox proportional hazards model, nodal status and T stage remained significantly associated with survival (Table 4). The hazard ratio of the pN0 group compared with pNx was 0.59 ($p = 0.036$) when controlling for T stage and type of resection (sublobar, yes/no).

The 3-year survival of patients in the pN0 group who had only N1 LNs examined was 70%; for those with only N2 LNs examined, it was 77%; and it was 67% for those with both N1 and N2 LNs examined. The survival experience of these groups was not significantly different ($p = 0.53$). There remained no difference even after adjustment for T stage. In the multiple variable analysis, T stage was significantly associated with outcome ($p < 0.01$). Neither the location of LNs examined (N1 only, N2 only, or N1 and N2) nor the extent of resection was a significant determinant of outcome.

# CONCLUSIONS

We created the MMA-QSR cohort to enable us closely examine the factors that underlie the reported variation in quality and outcomes of surgical resection for lung cancer, as part of a much-needed national quality-improvement process in lung cancer care.[21] Our cohort is comparable with the

**TABLE 2.** Details of Lymph Node Examination in pN0 Cohort

| Lymph Node Examination Parameter | Median (Range) | *N* with Parameter | Percent |
|---|---|---|---|
| All lymph node stations | 5 (1–45) | 506 | 100 |
| Peripheral nodes (N1) | 3 (0–38) | | |
| Mediastinal nodes (N2) | 1 (0–29) | | |
| Only N1 nodes examined | 3 (1–18) | 179 | 35.4 |
| Only N2 nodes examined | 2 (1–13) | 46 | 9.1 |
| Both N1 and N2 nodes examined | 7 (2–45) | 281 | 55.5 |
| Total no. lymph nodes | | | |
| 1–10 | | 430 | 85.0 |
| 11–14 | | 47 | 9.3 |
| 15–16 | | 9 | 1.8 |
| >16 | | 20 | 4.0 |

**TABLE 3.** Stage-Dependent Survival Estimates

| Stage Group (*N*) | Survival Estimates (Standard Error) 1 Year | 2 Year | 3 Year | Log-Rank *p* |
|---|---|---|---|---|
| T1NXMX (54) | 0.83 (0.05) | 0.74 (0.06) | 0.70 (0.07) | 0.0113 |
| T2NXMX (12) | 0.58 (0.14) | 0.50 (0.14) | 0.25 (0.19) | |
| T1N0MX (221) | 0.88 (0.02) | 0.82 (0.03) | 0.79 (0.03) | 0.001 |
| T2N0MX (182) | 0.81 (0.03) | 0.72 (0.04) | 0.65 (0.04) | |
| T3N0MX (17) | 0.65 (0.12) | 0.65 (0.12) | 0.65 (0.12) | |
| T4N0MX (32) | 0.72 (0.08) | 0.60 (0.09) | 0.44 (0.10) | |
| T1NXMX (54) | 0.83 (0.05) | 0.74 (0.06) | 0.70 (0.07) | 0.17 |
| T1N0MX (221) | 0.88 (0.02) | 0.82 (0.03) | 0.79 (0.03) | |
| T2NXMX (12) | 0.58 (0.14) | 0.50 (0.14) | 0.25 (0.19) | 0.0086 |
| T2N0MX (182) | 0.81 (0.03) | 0.72 (0.04) | 0.65 (0.04) | |

Copyright © 2010 by the International Association for the Study of Lung Cancer


Copyright © 2010 by the International Association for the Study of Lung Cancer.

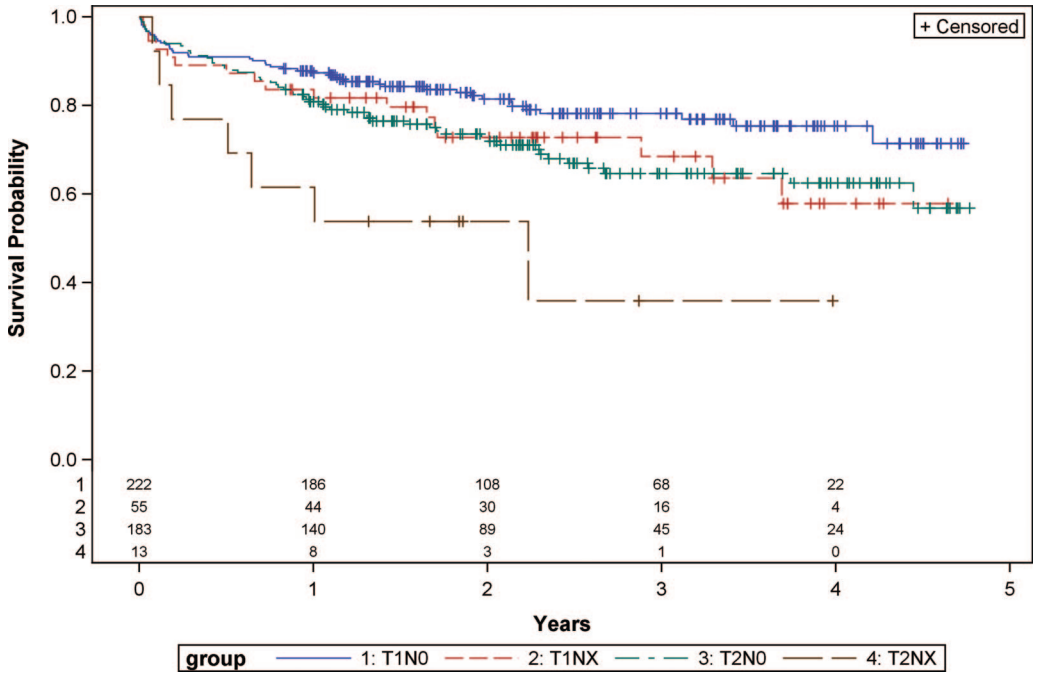


**FIGURE 1.** Kaplan-Meier survival curves for patients with T1N0, T1Nx, T2N0, and T2Nx non-small cell lung cancer in the Memphis Metropolitan Area Quality of Surgical Resection cohort.

**TABLE 4.** Multivariate Analysis of Survival Differences

| Multiple Variable Cox PH Model | |
|---|---|
| **Variable** | ***p*** |
| Survival comparisons between pN0 and pNx | |
| N0/NX | 0.0363 |
| T stage | 0.0012 |
| Sublobar (yes/no) | 0.65 |
| Survival comparisons between pN0 patients with N1 only, N2 only and N1 + N2 nodes | |
| Level 1 only/level 2 only/levels 1 and 2 | 0.80 |
| T stage | 0.0031 |
| Sublobar (yes/no) | 0.82 |

general population of patients undergoing surgical resection for NSCLC in the United States. The demographic characteristics are similar, except for the higher proportion of black patients, which reflects the demographic features of a southern U.S. population.[16,21] However, unlike the general U.S. experience in which 24 to 36% of all lung resections are performed by general surgeons,[22,23] all patients in the MMA-QSR cohort had their resection performed by board-certified cardiothoracic or general thoracic surgeons. This suggests that the overall quality of resection is likely no worse than in the average U.S. population. Indeed, the impact of surgeon specialty on short and long-term survival is such that our cohort might even be better.[22–24]

A comparison of key quality resection parameters in the MMA-QSR pN0/pNx cohort to a National Cancer Database (NCDB) cohort[21] with stage I disease shows that our pneumonectomy (6.7% versus 7.7%) and wedge resection (11.1% versus 17.1%) rates are comparable. Although it is alarming that 45% of our pNx/pN0 cohort had no mediastinal LNs examined, this is similar to the NCDB data in which 42.2% of the whole cohort had the same problem. Indeed, the full MMA-QSR cohort in which 30.8% did not have mediastinal LNs examined compares favorably with the broader U.S. experience reported by the NCDB.

In a landmark retrospective analysis of the Surveillance, Epidemiology and End-Results (SEER) database, in which all patients with pNx disease were excluded, Ludwig et al. found an increase in survival with increasing number of LNs evaluated after definitive surgery for stage I NSCLC, with a peak at about 13 to 16 LNs. They suggested that between 11 and 16 LNs need to be evaluated to assure node negativity.[16] In this SEER cohort, 41.8% had 1 to 4 LNs, 72.1% had 1 to 8 LNs, 14.7% had 9 to 12, and 5.8% had 13 to 16 LNs examined. In our pN0 cohort, 43.3% had 1 to 4; 75.9% had 1 to 8; 15.0% had 9 to 12; and 5.1% had 13 to 16 LNs examined. It seems, therefore, that the MMA-QSR cohort is reasonably reflective of the U.S. experience and our findings are likely to be generalizable.

It is disappointing that 12% of patients undergoing surgical resection for NSCLC have no LNs examined. It is interesting that most of these patients had a sublobar resection. It is equally interesting to note that a significantly higher percentage of patients in the pNx group had T1 lesions, compared with pN0 patients. It is not clear whether this reflects a practice of limiting the extent of lung resection because of limited residual lung function and/or excessive comorbidity, or whether there is a practice trend to perform sublobar resections in patients with relatively smaller lesions,


Copyright © 2010 by the International Association for the Study of Lung Cancer

Copyright © 2010 by the International Association for the Study of Lung Cancer.

or both. Unfortunately, we did not have access to preoperative pulmonary function studies that would have enabled us to examine for any differences in pulmonary function between the two groups. However, all demographic characteristics, including age, race, and gender, which may be associated with comorbid risk, were similar between the two groups of patients (Table 1).

Our findings are very similar to those of Varlotto et al.[25] in their retrospective review of patients in the SEER database who had resection for stage I NSCLC from 1992 to 2002, in which they found that 13% had pNx. Seventy percent of this cohort had received sublobar resection and the median lesion size of this group (20 mm) was significantly less than that of the full pN0 cohort (25 mm). Furthermore, 49% of this SEER cohort had no mediastinal LN examination, similar to the 45% in the MMA-QSR cohort, and the median number of LNs examined in the pN0 cohort was 5, which is identical to our findings.

Although the Lung Cancer Study Group report that the outcome after sublobar lung resection is inferior to that after lobectomy led to the adoption of lobectomy as the recommended extent of resection,[15,26] there continues to be a debate in the thoracic surgery community about the role of sublobar resection in patients with small, peripheral lung cancers.[27,28] This is the focus of an ongoing Cancer and Leukemia Group B study (clinicaltrials.gov identifier NCT00499330). Until results of this trial are available, it seems prudent to recommend lobectomy as the resection extent of choice for lung cancer, except in the case of limited lung function. However, even patients who undergo sublobar resections should have thorough evaluation of their LNs to the same extent as those with lobectomy. The safety of LN dissection or sampling in patients who have limited lung function is not of major concern. Comorbidity and limited lung function do not significantly alter either the risk or benefit of adequate lymph nodal examination in patients who undergo a wedge resection for NSCLC. Our findings may indicate misunderstanding of the need for LN examination in all patients who undergo potentially curative surgery for lung cancer.

Our study also points to the potential involvement of pathologists in the problem of suboptimal LN staging. Patients who have adequate lung tissue resected to assure the presence of intrapulmonary LNs would be expected to have those nodes available for examination, even if the surgeon did not dissect them out of the submitted resection material. Pathologists are expected to specifically seek these out. We found a large proportion of cases (44% of pNx and 9% of pN0) in which the pathologist did not search for such LNs. This is significant because it points to an opportunity for successful intervention in the pathology laboratory.

In the end, our most important finding is the disparity in survival between the two cohorts. Comparison of the 3-year survival of the MMA-QSR cohort with the cohort of Clifton Mountain that was used to develop the sixth AJCC lung cancer staging criteria[7] is very instructive. The MMA-QSR pT1N0M0 survival estimate (79%) is similar to the Mountain cohort (80%); as is pT2N0M0 (65%, MMA versus 67%, Mountain). This corroborates our earlier argument that the MMA-QSR cohort approximates the general U.S. experience. The survival of the T1NxM0 group (70%) is closer to that of T2N0M0 group of Mountain. The survival (25%) of T2NxM0 group is worse than that of T1–3N2M0 cohort (32%) of Mountain. This observation may be explained by the fact that about 46% of patients with pT2 NSCLC who undergo careful LN examination have node-positive disease, including 24% with N2 disease; 29% of those with pT1 have nodal involvement, 19% having pN1, and 10% pN2 disease.[9] However, it is also possible that the pNx group had significantly worse lung function, which was why so many of them had sublobar resection in the first place. It is also possible that they had other unexplained significant comorbidities that account for their higher mortality rate. However, it is notable that the 30-day postoperative mortality rate was identical between the two groups, as well as key demographic characteristics such as age, gender, and race, that can point indirectly to the likelihood of comorbidity. However, updates of the MMA-QSR database will attempt to incorporate information on comorbidities and preoperative pulmonary function in a bid to adjust future analyses for preoperative risk.

Nodal staging of patients in the MMA-QSR cohort was very poor. Neither demographic nor disease factors account for this. The failure to show a difference in outcomes between the pN0 patients who had only N1 or N2 or both N1 and N2 LNs examined, although somewhat surprising, may simply reflect this fact. The low number of LNs examined suggests that the predominant type of intraoperative LN examination procedure was random sampling, which is known to yield outcomes inferior to those of systematic sampling or complete mediastinal LN dissection.[29] Indeed, the median number of LNs examined in the pN0 group (five) is less than the minimum recommended by the International Association for the Study of Lung Cancer in the seventh AJCC staging system (six). It is significantly less than the evidence that suggests that the optimum number of LNs required to declare node negativity after resection of NSCLC is in the range of 11 to 16.[16,25] Thus, small, innocuous-looking LNs with metastases may have been left behind in each of the subgroups of patients with pN0, thereby negating the effect of sampling location.

The use of wedge resection is frequently associated with failure to identify LNs for examination. However, 45% of patients in the pNx group had received a lobectomy or bilobectomy, which suggests that pathologists also fail to isolate LNs for examination from adequately resected specimens. Most patients with node-negative disease have fewer than 10 nodes, and a large proportion have no mediastinal LNs examined (Table 2). This raises the possibility of understaging.

Patients with pT2 NSCLC who have surgical resection without LN examination are an especially vulnerable population. Estimation of their prognosis should take this fact into account. Their postoperative management should be designed to mitigate the danger from the high risk of undiagnosed LN involvement.

## ACKNOWLEDGMENTS

*Supported by OSI Pharmaceuticals, Inc. (to R.U.O.).*

*The authors thank Matthew P. Smeltzer for assistance with statistical analysis and Mathew Ninan for technical advice.*

*Copyright © 2010 by the International Association for the Study of Lung Cancer*



Copyright © 2010 by the International Association for the Study of Lung Cancer.

## REFERENCES


1. Rusch VW, Crowley J, Giroux DJ, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the N descriptors in the forthcoming seventh edition of the TNM classification for lung cancer. *J Thorac Oncol* 2007;2:603–612.
2. D'Cunha J, Herndon JE II, Herzan DL, et al. Poor correspondence between clinical and pathologic staging in stage 1 non-small cell lung cancer: results from CALGB 9761, a prospective trial. *Lung Cancer* 2005;48:241–246.
3. Lee PC, Port JL, Korst RJ, et al. Risk factors for occult mediastinal metastases in clinical stage I non-small cell lung cancer. *Ann Thorac Surg* 2007;84:177–1781.
4. Silvestri GA, Gould MK, Margolis ML, et al; American College of Chest Physicians. Noninvasive staging of non-small cell lung cancer: ACCP evidenced-based clinical practice guidelines (2nd edition). *Chest* 2007; 132(3 Suppl):178S–201S.
5. Tournoy KG, Maddens S, Gosselin R, et al. Integrated FDG-PET/CT does not make invasive staging of the intrathoracic lymph nodes in non-small cell lung cancer redundant: a prospective study. *Thorax* 2007;62:696–701.
6. Roberts JR, Blum MG, Arildsen R, et al. Prospective comparison of radiologic, thoracoscopic, and pathologic staging in patients with early non-small cell lung cancer. *Ann Thorac Surg* 1999;68:1154–1158.
7. Mountain CF. Revisions in the international system for staging lung cancer. *Chest* 1997;111:1710–1717.
8. Rami-Porta R, Ball D, Crowley J, et al; International Staging Committee; Cancer Research and Biostatistics; Observers to the Committee; Participating Institutions. The IASLC Lung Cancer Staging Project: proposals for the revision of the T descriptors in the forthcoming (seventh) edition of the TNM classification for lung cancer. *J Thorac Oncol* 2007;2:593–602.
9. Graham AN, Chan KJ, Pastorino U, et al. Systematic nodal dissection in the intrathoracic staging of patients with non-small cell lung cancer. *J Thorac Cardiovasc Surg* 1999;117:246–251.
10. Veeramachaneni NK, Battafarano RJ, Meyers BF, et al. Risk factors for occult nodal metastasis in clinical T1N0 lung cancer: a negative impact on survival. *Eur J Cardiothorac Surg* 2008;33:466–469.
11. Ikeda K, Nomori H, Mori T, et al. Size of metastatic and nonmetastatic mediastinal lymph nodes in non-small cell lung cancer. *J Thorac Oncol* 2006;1:949–952.
12. Prenzel KL, Mönig SP, Sinning JM, et al. Lymph node size and metastatic infiltration in non-small cell lung cancer. *Chest* 2003;123: 463–467.
13. Suzuki K, Nagai K, Yoshida J, et al. Predictors of lymph node and intrapulmonary metastasis in clinical stage IA non-small cell lung carcinoma. *Ann Thorac Surg* 2001;72:352–356.
14. Ohta Y, Oda M, Wu J, et al. Can tumor size be a guide for limited surgical intervention in patients with peripheral non-small cell lung cancer? Assessment from the point of view of nodal micrometastasis. *J Thorac Cardiovasc Surg* 2001;122:900–906.
15. Scott WJ, Howington J, Feigenberg S, et al; American College of Chest Physicians. Treatment of non-small cell lung cancer stage I and stage II: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest* 2007; 132(3 Suppl):234S–242S.
16. Ludwig MS, Goodman M, Miller DL, et al. Postoperative survival and the number of lymph nodes sampled during resection of node-negative non-small cell lung cancer. *Chest* 2005;128:1545–1550.
17. Ou SH, Zell JA. Prognostic significance of the number of lymph nodes removed at lobectomy in stage IA non-small cell lung cancer. *J Thorac Oncol* 2008;3:880–886.
18. Fukui T, Mori S, Yokoi K, et al. Significance of the number of positive lymph nodes in resected non-small cell lung cancer. *J Thorac Oncol* 2006;1:120–125.
19. Lee JG, Lee CY, Park IK, et al. Number of metastatic lymph nodes in resected non-small cell lung cancer predicts patient survival. *Ann Thorac Surg* 2008;85:211–215.
20. Kang CH, Ra YJ, Kim YT, et al. The impact of multiple metastatic nodal stations on survival in patients with resectable N1 and N2 nonsmall-cell lung cancer. *Ann Thorac Surg* 2008;86:1092–1097.
21. Little AG, Rusch VW, Bonner JA, et al. Patterns of surgical care of lung cancer patients. *Ann Thorac Surg* 2005;80:2051–2056; discussion 2056.
22. Farjah F, Flum DR, Varghese TK Jr, et al. Surgeon specialty and long-term survival after pulmonary resection for lung cancer. *Ann Thorac Surg* 2009;87:995–1004; discussion 1005–1006.
23. Goodney PP, Lucas FL, Stukel TA, et al. Surgeon specialty and operative mortality with lung resection. *Ann Surg* 2005;241:179–184.
24. Silvestri GA, Handy J, Lackland D, et al. Specialists achieve better outcomes than generalists for lung cancer surgery. *Chest* 1998;114:675–680.
25. Varlotto JM, Recht A, Nikolov M, et al. Extent of lymphadenectomy and outcome for patients with stage I nonsmall cell lung cancer. *Cancer* 2009;115:851–858.
26. Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. *Ann Thorac Surg* 1995;60:615–622; discussion 622–623.
27. Mery CM, Pappas AN, Bueno R, et al. Similar long-term survival of elderly patients with non-small cell lung cancer treated with lobectomy or wedge resection within the surveillance, epidemiology, and end results database. *Chest* 2005;128:237–245.
28. Schuchert MJ, Pettiford BL, Keeley S, et al. Anatomic segmentectomy in the treatment of stage I non-small cell lung cancer. *Ann Thorac Surg* 2007;84:926–932; discussion 932–933.
29. Gajra A, Newman N, Gamble GP, et al. Effect of number of lymph nodes sampled on outcome in patients with stage I non-small-cell lung cancer. *J Clin Oncol* 2003;21:1029–1034.



*Copyright © 2010 by the International Association for the Study of Lung Cancer*

Copyright © 2010 by the International Association for the Study of Lung Cancer.